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Applicants : Solo Goldstein, Claude Guillonneau, Yves Charton, Brian Lockhart, and Pierre Lestage

Title : "1,1- and 1,2-disubstituted cyclopropane compounds"

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Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

As soon as the Serial No. and Filing Date have been accorded the above-identified application, kindly enter the following amendment:

IN THE ABSTRACT: Kindly replace the Abstract, page 68, with the substitute Abstract sheet page 8 provided herewith.

IN THE CLAIMS: Kindly cancel claims 1-18 and replace with the following claims 19-36, which correspond to each cancelled claim.

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REMARKS:

A few constructive editorial changes have been made in the claims to bring them somewhat more into line with U.S. practice and requirements.

Applicants have cancelled all of the originally filed claims, 1-18. New claims 19-36 have been added to better encompass the full scope and breadth of the invention, notwithstanding Applicants' belief that the claims would have been allowable as originally filed. Accordingly, Applicants assert that no claims have been narrowed within the meaning of Festo .

Entry of the amendments and a swift and favorable action on the merits are all hereby respectfully solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

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Enclosure: Return Postal Card Receipt
New Claims 19-36 and New Abstract

CLAIMS

19 A compound selected from those of formula (I) :

(I),

wherein :

p represents an integer of from 0 to 6 inclusive,

n represents an integer of from 0 to 6 inclusive,

R_1 and R_2, which may be identical or different, each independently of the other represent a group selected from hydrogen, linear or branched (C_1-C_6)alkyl, aryl, and aryl-(C_1-C_6)alkyl in which alkyl is linear or branched, or R_1+R_2 form together with the nitrogen carrying them saturated, a 3- to 10-membered, monocyclic, or bicyclic system, optionally containing a second hetero atom selected from oxygen, nitrogen, and sulphur,

X represents a group selected from oxygen, sulphur, -CH=CH-, methylene, a group of formula -HC=N-O- and a group of formula -O-CH_2-CH=CH-, in which groups oxygen is linked to Y of formula (I),

Y represents a group selected from aryl, heteroaryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, heteroaryl-(C_1-C_6)alkyl in which alkyl is linear or branched, -C(O)-A, and -C(S)-A,

A represents a group selected from linear or branched (C_1-C_6)alkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl in which alkyl is linear or branched, heteroaryl-(C_1-C_6)alkyl in which alkyl is linear or branched, and NR_3R_4 wherein R_3, and R_4, which may be identical or different, each represent a group selected from hydrogen, linear or branched (C_1-C_6)alkyl, aryl, and aryl-(C_1-C_6)alkyl in which alkyl is linear or branched, or R_3+R_4 form together with nitrogen carrying them a monocyclic, or bicyclic (C_3-C_{10}) system,

its isomers and addition salts thereof with a pharmaceutically-acceptable acid or base,

with the proviso that :

- *in the case of 1,1-disubstituted compounds of formula (I),*

- p is other than zero, when X represents methylene, n has the value zero, Y represents aryl, or heteroaryl, and R_1, and R_2, which may be identical or different, represent hydrogen, linear or branched (C_1-C_4)alkyl, benzyl, phenylethyl, or form together with the nitrogen carrying them morpholino, thiomorpholino, or a 5- to 7-membered saturated carbocyclic system,
- p is other than zero, when X represents methylene, n has the value zero, Y represents acetyl, and R_1, and R_2, which may be identical or different, represent hydrogen, linear or branched (C_1-C_4)alkyl, phenyl, benzyl, or form together with the nitrogen carrying them piperidyl, or morpholino,
- R_1, and R_2 do not simultaneously represent methyl:
  * either, when p, and n each have the value 1, X represents oxygen, and Y is selected from p-nitrobenzoyl, p-aminobenzoyl, p-chlorophenylaminocarbonyl, and acetyl,
  * or, when p has the value zero, n has the value 1, X represents oxygen, or sulphur, and Y represents 2-quinolyl substituted in the 3-position by linear or branched (C_3-C_4)alkyl, or phenyl,
- Y does not represent 1,2-benzisoxazol-3-yl when n has the value 1, p has the value zero, and X represents oxygen,

♦ *in the case of 1,2-disubstituted compounds of formula (I),*

- R_1, and R_2 do not simultaneously represent hydrogen when p, and n each have the value zero, and X-Y together represent phenoxy (optionally substituted by one or two, identical or different, groups selected from methoxy, dimethylamino, halogen, methyl, trifluoromethyl, nitro, and amino), phenylsulphanyl, benzyloxy, benzyl, or 2-phenylethyl,
- R_1 and R_2 do not simultaneously represent methyl when p, and n each have the value zero and X-Y together represent phenoxy (optionally substituted by a group selected from chlorine, and trifluoromethyl), phenylsulphanyl, or benzyl,

and also with the proviso that the compounds of formula (I) are other than the following compounds :

- (1-benzylcyclopropyl)methanamine,
- (1-benzylcyclopropyl)-N,N-dimethylmethanamine,

- 2-(phenoxycyclopropyl)methanamine,
- 2-(phenoxymethyl)-cyclopropanamine,
- (N,N-dimethyl)-2-(acetoxymethyl)-cyclopropanemethanamine,
- N-{2-[2-(benzyloxy)ethyl]cyclopropyl}-N,N-dimethylamine.

it also being understood that :

- aryl denotes phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indanyl, or indenyl, each of those groups being optionally substituted by one or more, identical or different, groups selected from halogen, linear or branched (C_1-C_6)alkyl, hydroxy, cyano, nitro, linear or branched (C_1-C_6)alkoxy, linear or branched (C_2-C_7)acyl, linear or branched (C_1-C_6)alkoxycarbonyl, linear or branched (C_1-C_6)trihaloalkyl, linear or branched (C_1-C_6)trihaloalkoxy, and amino optionally substituted by one or two linear or branched (C_1-C_6)alkyl,

- heteroaryl denotes 5- to 12-membered, monocyclic aromatic or bicyclic system containing from one to three, identical or different, hetero atoms selected from oxygen, nitrogen and sulphur, one of the rings of which, in the case of bicyclic system, is aromatic in character, and the other ring of which may be aromatic, or partially hydrogenated, each of those groups being optionally substituted by one or more, identical or different, groups selected from substituents defined hereinbefore for aryl.

20 -A compound of claim 19, wherein n is an integer of from 0 to 2 inclusive.

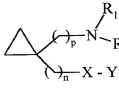
21- A compound of claim 19, wherein R_1, and R_2, which may be identical or different, each represent hydrogen, or linear or branched (C_1-C_6)alkyl.

22- A compound of claim 19, wherein X represents oxygen.

23- A compound of claim 19, wherein Y represents a group selected from -C(O)NR_3R_4 wherein R_3, and R_4, are as defined for formula (I), acetyl, -C(O)-heteroaryl, aryl-(C_1-C_6)alkyl in which alkyl is linear or branched, and heteroaryl.

24- A compound of claim 19, wherein Y represents pyridyl.

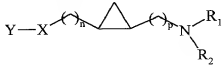
25- A compound of claim 19, Which is a compound of formula **(IA)** :



(IA),

wherein n, p, X, Y, R_1 and R_2 are as defined for formula (I), its isomers and addition salts thereof with a pharmaceutically-acceptable acid or base.

26- A compound of claim 19, which is a compound of formula **(IB)** :



(IB),

wherein n, p, X, Y, R_1, and R_2 are as defined for formula (I), its isomers and addition salts thereof with a pharmaceutically-acceptable acid or base.

27- A compound of claim 19, wherein p is an integer having the value 0 or 1.

28- A compound of claim 26, wherein p represents 0, or 1, n represents 0, or 1, R_1 and R_2, which may be identical or different, represent hydrogen, or linear or branched (C_1-C_6)alkyl, X represents oxygen, and Y represents a group selected from phenyl-(C_1-C_6)alkyl in which alkyl is linear or branched, pyridyl, and -C(O)-A wherein A represents linear or branched (C_1-C_6)alkyl, mono(C_1-C_6)alkylamino, or di(C_1-C_6)alkylamino, alkyl being linear or branched, its isomers and addition salts thereof with a pharmaceutically-acceptable acid or base.

29- A compound of claim 25, wherein p represents 0, or 1, n is an integer of from 0 to 3 inclusive, R_1 and R_2, which may be identical or different, represent hydrogen, linear or branched (C_1-C_6)alkyl or form together with nitrogen carrying them a pyrrolidinyl group, X represents oxygen, sulphur or -CH=CH-, and Y represents a group selected from phenyl (optionally substituted by hydroxy, linear or branched (C_1-C_6)alkyl or halogen), pyridyl,

pyridyl-(C_1-C_6)alkyl in which alkyl is linear or branched (pyridyl in each of those groups being optionally substituted by a group selected from halogen, and linear or branched (C_1-C_6)alkyl), and -C(O)-A wherein A represents a group selected from linear or branched (C_1-C_6)alkyl, linear or branched mono(C_1-C_6)alkylamino, linear or branched di(C_1-C_6)alkylamino, and pyridyl, its isomers and addition salts thereof with a pharmaceutically-acceptable acid or base.

30- A compound of claim 19, which is selected from :

- 2-[1-(dimethylamino)cyclopropyl]ethyl methylcarbamate,
- 2-[1-(dimethylamino)cyclopropyl]ethyl dimethylcarbamate,
- [1-(dimethylamino)cyclopropyl]methyl dimethylcarbamate,
- [1-(dimethylamino)cyclopropyl]methyl acetate,
- 2-[1-(dimethylamino)cyclopropyl]ethyl acetate,
- 1-[(dimethylamino)methyl]cyclopropyl acetate,
- [1-(dimethylamino)cyclopropyl]methyl nicotinate,
- *N*,*N*-dimethyl-1-[(3-pyridyloxy)methyl]cyclopropanamine,
- *N*-methyl-1-[(3-pyridyloxy)methyl]cyclopropanamine,
- *N*,*N*-dimethyl-1-[(3-pyridylmethoxy)methyl]cyclopropanamine,
- *N*,*N*-dimethyl-1-[2-(3-pyridyloxy)ethyl]cyclopropanamine,
- 4-({2-[1-dimethylamino)cyclopropyl]ethyl}sulphanyl)phenol,
- (±)-*cis*-2-(dimethylamino)cyclopropyl methylcarbamate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl methylcarbamate,
- (±)-*cis*-2-(dimethylamino)cyclopropyl acetate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl acetate,
- (±)-*cis*-2-(dimethylamino)cyclopropyl]methyl acetate,
- (±)-*trans*-2-(dimethylamino)cyclopropyl]methyl acetate,
- (±)-*cis*-2-[(benzyloxy)methyl]-*N*,*N*-dimethylcyclopropanamine,
- (±)-*trans*-2-[(benzyloxy)methyl]-*N*,*N*-dimethylcyclopropanamine,
- (±)-*trans*-2-[(dimethylamino)methyl]cyclopropyl acetate,
- 1-[(3-pyridyloxy)methyl]cyclopropanamine dihydrochloride,
- *N*-methyl-1-{[(6-methyl-3-pyridyl)oxy]methyl}cyclopropanamine hydrochloride,
- *N*-methyl-1-{[(6-chloro-3-pyridyl)oxy]methyl}cyclopropanamine hydrochloride,

- *N*-{1-[(3-fluorophenoxy)methyl]cyclopropyl}-*N*-methylamine hydrochloride,
- 3-[1-(dimethylamino)cyclopropyl]propyl dimethylcarbamate fumarate,
- 3-[1-(dimethylamino)cyclopropyl]propyl methylcarbamate fumarate,
- *N*-methyl-1-[(2-pyridylsulphanyl)methyl]cyclopropanamine dihydrochloride,
- *N*-methyl-1-[3-(3-pyridyloxy)propyl]cyclopropanamine dihydrochloride,
- *N*-methyl-1-[2-(3-pyridyl)ethyl]cyclopropanamine dihydrochloride,
- *N*-methyl-1-[(Z)-2-(3-pyridyl)ethenyl]cyclopropanamine fumarate,
- [1-(1-pyrrolidinyl)cyclopropyl]methyl dimethylcarbamate fumarate,
- *N,N*-dimethyl-1-[2-(3-pyridyl)ethyl]cyclopropanamine hydrochloride,
- 3-{[1-(1-pyrrolidinyl)cyclopropyl]methoxy}pyridine fumarate,
- *N*-methyl-1-[2-(3-pyridyloxy)ethyl]cyclopropanamine fumarate,
- 2-[1-(methylamino)cyclopropyl]ethyl dimethylcarbamate hydrochloride, and
- 2-[1-(1-pyrrolidinyl)cyclopropyl]ethyl dimethylcarbamate fumarate,

its isomers and addition salts thereof with a pharmaceutically-acceptable acid or base.

31- A method for treating a living animal body afflicted with a condition where specific nicotinic ligands of $\alpha_4\beta_2$ receptors are involved, comprising the step of administering to the living animal body an amount of a compound of claim 19 which is effective for alleviation of said condition.

32- A method for treating a living animal body afflicted with deficiencis of memory associated with cerebral aging and with neurodegenerative disease, or with a mood disorder disease, Tourette's syndrome, hyperactivity syndrome with attention-deficit, tobacco withdrawal, or pain, comprising the step of administering to the living animal body an amount of a compound of claim 19 which is effective for alleviation of said conditions.

33- A method for treating a living animal body afflicted with deficiencies of memory associated with Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, or frontal lobe and subcortical dementias, comprising the step of administering to the living animal body an amount of a compound of claim 19 which is effective for

alleviation of said conditions.

34- A pharmaceutical composition useful as specific nicotinic ligands of $\alpha_4\beta_2$ receptors, comprising as active principle an effective amount of a compound as claimed in claim 19, alone or in combination with one or more pharmaceutically-acceptable excipients or carriers.

35- A pharmaceutical composition useful for treating a living animal body afflicted with deficiencis of memory associated with cerebral aging and with neurodegenerative disease, or with a mood disorder disease, Tourette's syndrome, hyperactivity syndrome with attention-deficit, tobacco withdrawal, or pain, comprising as active principle an effective amount of a compound as claimed in claim 19, together with one or more pharmaceutically-acceptable excipients or vehicles.

36- A pharmaceutical composition useful for treating a living animal body afflicted with deficiencies of memory associated with Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, or frontal lobe and subcortical dementias, comprising as active principle an effective amount of a compound as claimed in claim 19, together with one or more pharmaceutically-acceptable excipients or vehicles.

ABSTRACT OF THE DISCLOSURE

A compound selected from those of formula (I) :

(I),

wherein :

p represents an integer of from 0 to 6 inclusive,

n represents an integer of from 0 to 6 inclusive,

R_1, and R_2 represent a group selected from hydrogen, alkyl, aryl and arylalkyl, or R_1+R_2 form together with nitrogen carrying them saturated, monocyclic, or bicyclic system,

X represents a group selected from oxygen, sulphur, a group -CH=CH-, methylene, a group of formula -HC=N-O- and a group of formula -O-CH_2-CH=CH-, in which groups oxygen is linked to Y of the compounds of formula (I),

Y represents a group selected from aryl, heteroaryl, arylalkyl, heteroarylalkyl, -C(O)-A, and -C(S)-A,

A represents a group selected from alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, and NR_3R_4 wherein R_3, and R_4 represent a group selected from hydrogen, alkyl, aryl, and arylalkyl, or R_3+R_4 form together with nitrogen carrying them monocyclic, or bicyclic (C_3-C_{10}) system,

its isomers and addition salts thereof with a pharmaceutically-acceptable acid or base, and medicinal products containing the same which are useful as specific nicotinic ligands of $\alpha_4\beta_2$ receptors.